Exhibit E

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 3 Cases*	

EXPERT REPORT OF WENXIN ZHENG, M.D.

EXPERT REPORT
WENXIN ZHENG, MD
Professor of Pathology
Professor of Obstetrics and Gynecology,
Director of Gynecologic Pathology,
University of Texas Southwestern Medical Center
JUNE 3, 2016

I. GENERAL OPINION

a. EDUCATION AND PROFESSIONAL EXPERIENCE

I was born in China, where I attended medical school and received my training in obstetrics and gynecology at Fudan University Shanghai Medical College. During my obstetrics and gynecology internship and residency, from 1982 to 1986, I observed and treated women with all sorts of obstetrics and gynecologic issues.

I came to the United States in 1986, where I completed my training in reproductive sciences research at Columbia University College of Physicians and Surgeons, from 1986 to 1991. I then completed a pathology residency at Cornell University – New York Hospital, from 1991 to 1995, where I also served as Chief Resident. I completed my training with a gynecologic pathology fellowship at Brown University – Women and Infants' Hospital, from 1995 to 1996. Following my gynecologic pathology fellowship, I joined the pathology and obstetrics/gynecology faculty at the School of Medicine at the University of Southern California. In 2000, I joined the pathology and obstetrics/gynecology faculty at Yale University School of Medicine, also serving as director of both Gynecologic Pathology and the Gynecologic Pathology fellowship at Yale. I left Yale, in 2005, to join the faculty at the College of Medicine at the University of Arizona. Meanwhile, I served as the Head of Department of Pathology, College of Medicine, Fudan University, China from 2005 to 2008. Starting from July 2015, I have relocated to University of Texas Southwestern Medical Center to serve to lead a gynecologic pathology program covering both Parkland Memorial Hospital and Clement University Hospital.

I am currently the Chief of Gynecologic Pathology at the University of Texas Southwestern Medical Center in Dallas, where I am also a tenured Professor of Pathology and a tenured Professor of Obstetrics/Gynecology with an endowed distinguished professorship in cancer research. In the early 1990's, I became interested in the most aggressive endometrial cancer – the uterine papillary serous carcinoma, which is now called endometrial serous carcinoma (ESC). I then devoted nearly 20 years to defining the pre-cancers of ESC and its carcinogenesis. My authority in endometrial serous carcinogenesis and pathology diagnosis of its pre-cancers is well recognized. In the late 1990's, I started to work on the hormonal etiology of sporadic ovarian epithelial cancer and provided direct evidence of gonadotropin FSH links to fallopian tube mucosa and ovarian epithelial cells. This project expanded to the study of serous carcinogenesis in the fallopian tube. My colleagues and I recently proposed that low-grade serous carcinomas of the ovary originate in the tubal epithelial cells through a secretory cell expansion process. Together with the findings that high-grade serous carcinomas of the ovary

mainly derive from fallopian tube, the majority of pelvic serous carcinomas are now considered as tubal origin.

In addition to my research, I direct a full-service of gynecologic pathology at the University of Texas Southwestern (UTSW) Medical Center and serve as an expert consultant for colleagues who have difficult cases, from the entire state of Texas, other states in the U.S., China, and many places in the world. I have published over 160 peer-reviewed articles in the field of gynecologic pathology and oncology. As a gynecologic pathologist, my routine work is to sign-out all gynecologic and obstetrics cases submitted to the Department of Pathology, UTSW Medical Center. Vaginal mesh related specimens are part of the general gynecologic cases I see. Upon receiving the mesh specimens, pathology residents or pathologist assistants will "gross in" them including the gross description (size, color, consistency, etc.), section them and conduct mesh-tissue processing. Microscopic slides are then made after paraffin embedding. I read the slides under a routine light microscope. For vaginal mesh specimens, I am typically looking for mesh like material induced spaces, inflammation (including the degree and the type of inflammation), foreign body granulomas, microorganisms, with or without squamous mucosa and anything that may be related to mesh/tissue reactions.

As a full professor, my academic responsibilities include medical student teaching, as well as graduate student, resident and fellow teaching in both pathology and obstetrics/gynecology. I have received several awards related to my teaching, including most recently in 2013: the John Davis Outstanding Residency Teaching Award, Department of Pathology, University of Arizona, and the Outstanding Overseas Teacher's Award, from the Department of Education, China.

I have served on the editorial board of several medical journals, including, for example, the American Journal of Cancer Research, International Journal of Clinical and Experimental Pathology, Journal of Cancer Research, and the Journal of Surgical Oncology. I am also Co-Editor-in-Chief of the American Journal of Clinical and Experimental Obstetrics and Gynecology. In addition, I have peer reviewed many scientific articles over the years, including for publication in Gynecologic Oncology, International Journal of Cancer, International Journal of Gynecologic Pathology, Journal of the National Cancer Institute, Human Pathology, Modern Pathology, American Journal of Surgical Pathology, and others.

My opinions that follow are held to a reasonable degree of medical and scientific certainty. Attached to this report are my curriculum vitae (Ex. A), which sets out my education and training in detail and lists my publications; a list of the materials I reviewed for this case and materials/exhibits which I will use to support my opinions (Ex. B., which among other things includes photographs, photomicrographs, and pathology slides I have reviewed); and my fee schedule based on the contract made between UTSW and the Butler Snow LLP (Ex. C) Also attached is a list of cases in which I have testified in the last four years (Ex. D). I expect to review the deposition transcripts of certain of plaintiffs' experts in these cases and may further develop my opinions after having done so.

b. IMPLANTED MESHES

The biocompatibility of long-term implantable medical devices is the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting much undesirable local or systemic effects in that host.[1] A small amount of inflammation near the interface between the foreign body and the tissue is related to better biocompatibility. A typical reaction to a biocompatible mesh is characterized by mild inflammation, foreign body giant cells, and mild to moderate degree of fibrosis. The presence of this reaction and its accompanying cells and their associated extracellular matrix (proteins outside of the cells) is expected following any tissue-damaging event, including surgery and the implantation of a device; it does not signal a problem with the device. The basic factors related to the overall biocompatibility of the mesh material are pore size, weight, elasticity and filament structure.

Today, polypropylene is the most widely used mesh material. Ethicon has produced polypropylene sutures for nearly 50 years. In 1975, it began using the same polypropylene material in knitted mesh, in its Prolene Mesh. Although Prolene Mesh was originally used for hernia repairs, Ethicon eventually created the TVT and TVT-O using the same Prolene Mesh, relying on over two decades of safe clinical application.

c. FOREIGN BODY RESPONSE

The human body's response to the presence of a foreign body is a well-known process that is taught to all physicians through a basic pathology course in medical school. Identification and microscopic analysis of this process is part of pathology training, which takes years of residency, fellowship, and pathologic practice to master. Even in the absence of an implanted foreign body, surgery will trigger the body's inflammatory response to repair the wound created by a surgical procedure. The aim or goal of this process is to eliminate the offending stimuli and to begin wound healing. After a device is implanted in the body, a cascade of inflammatory and wound healing processes is triggered. This cascade contains the hallmarks of a foreign body response. Several factors influence the scope and severity of the body's reaction to the implantation of a foreign body, including the level of trauma (e.g., tissue damage during surgery or suturing), biocompatibility of the implant, and the patient's unique exaggerated or suppressed response.

This response varies between patients. Some patients are predisposed to exaggerated immune and inflammatory responses, as well as scar formation, while others have a suppressed reaction. These reactions can be influenced by several factors, including the host's genetics and the host's other physical conditions or ailments (e.g., smoking, diabetes, etc.), regardless of whether a foreign body is implanted.

The inflammatory response begins within seconds to minutes of the offending injury or irritant. This is considered the acute inflammatory phase, predominated by neutrophils. If the process continues, it becomes a chronic process with hallmark characteristics of monocytes, macrophages, and fibroblasts.

Acute inflammatory response begins with an influx of blood plasma and leukocytes into the injured tissue. Neutrophils, with sacs containing enzymes to digest microorganisms, enter

the area to clear any foreign materials. These neutrophils are able to move between cells. This phase is responsible for cleaning the wound site and laying down a provisional matrix and proteins that provide support for the processes that follow. Cytokines, growth factors, and blood and tissue proteins are released. Monocytes are then signaled to the site by the presence of cytokines.

If the inflammation is prolonged and becomes a chronic process, which occurs with the presence of an implanted medical device, there is a shift in the type of cells found at the site of inflammation, namely to monocytes, macrophages and fibroblasts. These cells can be present at the site within a few days. Monocytes differentiate and become macrophages. Twenty-four hours after injury, the wound healing process begins with connective tissue and the formation of new blood vessels to nourish the new tissue (angiogenesis). This leads to the formation of granulation tissue, another stage of the foreign body reaction.

The function of the foreign body reaction is to eliminate or, where elimination is not possible, isolate the foreign body from the native tissue in which it is embedded. Macrophages "engulf" foreign materials and ingest them (also known as phagocytosis). If a material is too large for phagocytosis, several macrophages will sometimes fuse to form a foreign body giant cell in order to engulf the foreign material. When active, foreign body giant cells secrete superoxides and free radicals in an attempt to destroy the foreign material in order to digest or wipe them out completely. Foreign body giant cells are typically seen six to seven days following implantation of a foreign object.

In addition to phagocytosis, macrophages and foreign body giant cells, together with neovascularization, also play a role in the creation of granulation tissue through the stimulation of fibroblasts. The incoming fibroblasts work to lay down collagen fibers leading to an organized collagenous structure around the implant's structure. In the case of a mesh, this new tissue structure can integrate into the pores of the mesh (see below). Neovascularization occurs to provide nourishment to the new tissue. Fibrosis (scar formation), which varies in degree, is typically the last step in the foreign body reaction in the presence of an indigestible implant. Fibrosis and scar formation is also a part of normal process for wound healing either induced by surgery or injury.

d. TISSUE INTEGRATION

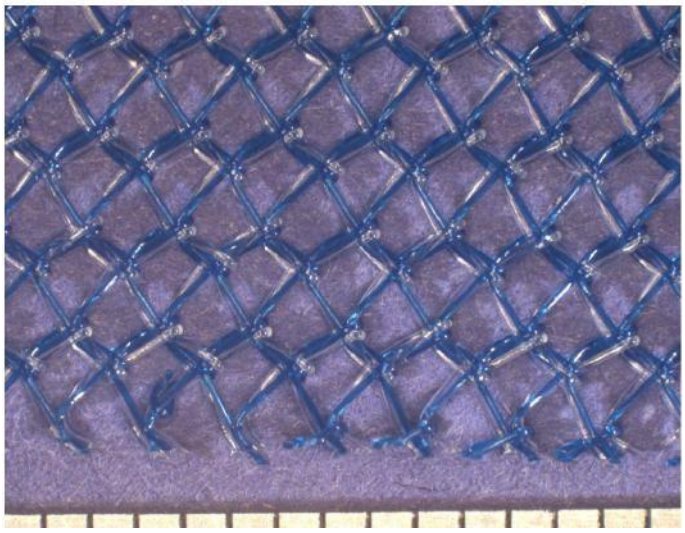
The integration of mesh by connective tissue surrounding the mesh filaments is important to provide support to the mesh. Thus, it is important for the mesh to allow tissue to grow into the pores between the mesh filaments. However, there is a balance between appropriate integration and excessive formation of scar tissue (see below), which is disfavored. During the tissue-generating portion of the foreign body response, mesh pores of a sufficient size permit tissue ingrowth. This occurs because the inflammatory response to the mesh material elicits the body's creation of new tissue. A mesh with appropriate pore size will allow the extracellular matrix and the cells necessary for the creation of new tissue to enter the pore spaces and fill them with the new connective tissue. When tissue is able to integrate into mesh pores, encapsulation does not occur like it can with solid implants or microporous meshes.[2] [3] [4]

In 1997, Dr. Amid set out surgical mesh pore size classifications that are widely accepted today. According to Dr. Amid, a mesh containing pores larger than 75 microns is a macroporous mesh, meaning the pores are large enough to allow macrophages, fibroblasts, neovasculature, and collagen, and sometimes nerve fibers to enter the pore.[5] Dr. Amid's classification is consistent with basic cell biology and the necessary responses to the implantation of a foreign body, and it is widely used.[6] [7] [8]

The cells and tissues involved in the foreign body response, tissue healing, and immune response are small: lymphocytes are 12-20 microns, neutrophils are 10-12 microns, monocytes are 12-20 microns, macrophages are 16-30 microns, foreign body giant cells vary from 30 microns to a few hundred, and fibroblasts are 10-25 microns. In between these cells, there are vessels and extracellular matrix. The extracellular matrix can vary depending on the density of the cells. As stated above, leukocytes and macrophages are an important part of the fibrosis process, and these cells can easily access pores larger than 75 microns to allow tissue ingrowth. These can then be followed by the new blood vessels that are small enough to access the pores. In addition, macrophage entry allows for clearance of any bacteria, and a macrophage's pseudopodia allow it to access even smaller spaces.

Dr. Amid classified Prolene Mesh as macroporous because its pores are well-beyond 75 microns.[9] An example of TVT mesh structure with pores larger than 1,000 microns (or 1 millimeter) is shown here (Figure 1).

Figure 1 – TVT Mesh Structure (millimeter ruler pictured at bottom).



e. INFECTION

Infection is different from inflammation. As previously discussed, inflammation is a normal response. An infection is related to a tissue response process induced by bacteria, fungus, or other infectious organisms. Infection is a recognized risk of any surgery. When infection occurs after surgery, it is mainly related to the patient's immune system, surgical

procedures, and environmental conditions. In the majority of situations, the causes for surgery related infections are identifiable and preventable in American hospitals.

Given that implanted meshes by their nature require surgery, the potential for infection is always present and considered. Favored materials are inert to infection (i.e., they do not potentiate infection). Pore size and the filament construction are two factors in determining whether a mesh potentiates infection. Macroporous meshes allow the entry of the cells responsible for the body's immune response.[10] As a result, macroporous meshes generally have no impact on infection – they allow the body's immune responsive cells to clear any infectious agent when incidentally present in the implanted area.[11] In addition to pore size, meshes that consist of monofilament polypropylene construction have been shown to reduce the risk of infection (compared to multifilament mesh).[12] [13] Ethicon's TVT and TVT-O meshes are made of monofilament polypropylene. Additionally, the body has complex defense mechanisms to fight bacteria (e.g., a macrophage's pseudopodia).

f. Opinions on Tissue Response to TVT and TVT-O

Ethicon's TVT and TVT-O are the standard of care for the treatment of stress urinary incontinence in women. They are supported by numerous randomized controlled trials and other clinical studies, 17-year follow-up data shows very high cure rates, they are backed by the American Urogynecologic Society, the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction, and the American Urological Association, and studies show very low complication rates. [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] If there truly were problems with infection, lack of tissue integration, abnormal inflammatory response, etc., this would not be the case. Likewise, in my experience with pelvic meshes, I have seen many meshes removed from asymptomatic patients and the explanted material shows no signs of infection, with only a minimal degree of inflammation. In contrast, I have also seen meshes taken out of patients with erosion that clearly shows more extensive inflammation with probable evidence of infection; with erosion and/or ulceration, the mesh has contacted the "outside world", therefore more extensive inflammation and potential infection is expected. Based on published literature, mesh erosion with TVT and TVT-O is rare.[26]

There are many factors contributing to the complications related to TVT or TVT-O mesh implantation. The main contributing factors in general include surgical skill, location of the implant, individual patient's physical, mental, and immune conditions, and the biocompatibility of the implanted material. In this report, I mainly describe the biocompatibility and tissue responses associated with Ethicon's TVT and TVT-O mesh; surgical procedure related complications are beyond the scope of my expert report.

i. Inflammation and Foreign Body Response

The Prolene mesh used in TVT and TVT-O evokes a minimal or mild acute inflammatory response that transitions to a minimal or mild chronic inflammation, with a minimal to mild fibrotic reaction and neovascularization. [27] [28] [29] [30] This tissue response triggers tissue ingrowth into the mesh pores, which is needed to support the mesh placement. This is a normal tissue response process to a persistent implantation of a biocompatible foreign material, and is

consistent with my experience with the many polypropylene vaginal meshes I have seen in the last three years. As such, this reaction would not typically lead to complications.

ii. APPROPRIATE TISSUE INTEGRATION

In my opinion, the Prolene mesh used in TVT and TVT-O contains pores that are adequate to allow the cells responsible for the immune and inflammatory responses to enter the mesh spaces. In addition, the pores are large enough to allow the cells and materials necessary for the foreign body reaction, formation of granulation tissue, and neovascularization to enter the pore space – all necessary for appropriate healing and support of the implant. This leads to appropriate integration of the host's cells and their associated extracellular matrix, neovascularization, and sometimes nerve fibers, into the mesh pores. The end result is the formation of minimal to mild fibrosis without mature scar formation and, therefore, the normal function of the implanted mesh maintains its desired function in vivo (see below for more).

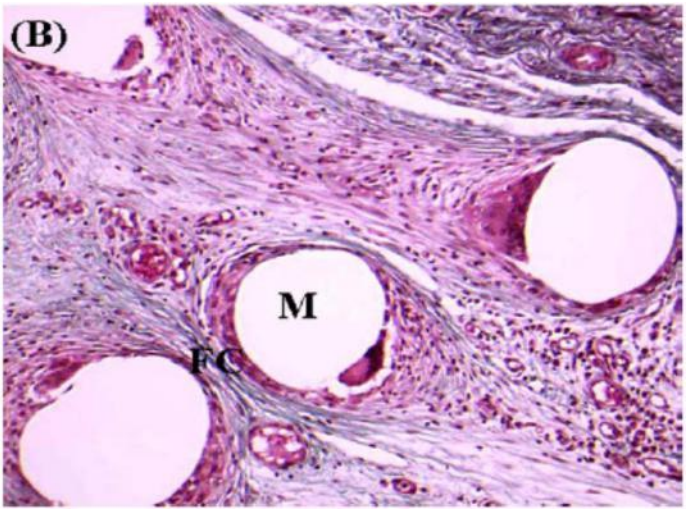
The Prolene mesh used in TVT and TVT-O contains pores that are larger than 1,000 microns. [31] This is several times larger than necessary to be considered a macroporous mesh (75 microns).[32] The cell sizes for all the relevant cells are much smaller than Prolene mesh's pore size. (Table 1). In my opinion, Prolene mesh's pores allow sufficient host cells, associated extracellular matrix, newly-formed blood vessels, and sometimes nerve endings to integrate into the mesh to allow for an appropriate inflammatory reaction, foreign body response, and tissue integration to support the mesh. (Figure 2).

Table 1. Cell Sizes.

Cell	**Size (microns)**
Neutrophil	10-12
Lymphocytes	12-20
Macrophage	16-30
Foreign body giant cell	30 to a few hundred
Fibroblast	10-25

As a result of the minimal to mild fibrosis and sufficient tissue integration into the Prolene mesh pores, it is my opinion that "scar-bridging" or encapsulation does not occur. My opinion is supported by the numerous clinical trials showing good performance and low complication rates with TVT and TVT-O [33] [34] [35] In addition, multiple animal studies also demonstrate TVT's sufficient pore size leading to appropriate tissue ingrowth. [36] [37] [38] Moreover, as discussed later, there was appropriate tissue ingrowth or integration in Ms. Hoch's case.

Figure 2 – Tissue Integration with Prolene Mesh. High magnification; the collagen fibers (FC) penetrate the inter filament spaces of the mesh (M) (light microscopy x100, Masson's trichrome).[39]



iii. INFECTION

The Prolene mesh used in TVT and TVT-O does not potentiate infection due to its material properties as well as its knitted structure. It is made of monofilament polypropylene, which does not promote infection. In addition, Prolene mesh's pores are sufficiently large to permit the entry of inflammatory and immune cells needed to eliminate bacteria or prevent bacterial colonization. This lack of infection potentiation is consistent with the years of safe use and multitude of studies showing low infection rates with TVT and TVT-O. [40] [41] [42] Plaintiffs' pathology expert, Dr. Iakovlev, agrees that the body's immune response can access "tight spaces to deliver their immune response."[43] As a result, the infection rate following the implantation of TVT or TVT-O should be minimal or negligible, within the acceptable range for implantation surgeries.

iv. FIBROSIS AND SCAR FORMATION

As discussed above, tissue integration occurs normally in the majority of implanted TVT and TVT-O meshes as soon as the surgical procedures are done properly and the tissue response to the implanted mesh are within normal range. Since one of the main cellular components in the integrated tissue is the fibroblast, some fibrosis is expected as a part of host-implant response. Scar formation is a process. It begins with fibroblasts producing collagen in the presence of components of healthy tissue, including extracellular matrix surrounding the cells and vessels, as well as possible nerve fibers. The process ends with pure but irregularly arranged collagen bundles without any cellular or vascular components as mature scar. Only those mature scars lose tissue elasticity and may change the shape or deform the tissue/organ depending on the amount and location of the mature scars, while immature scars, showing minimal, mild, or moderate fibrosis typically do not cause shape or functional change. Fibrous tissue is part of the connective tissue, which is present in normal vaginal wall tissue as well as in wound repair, while scar in general is the end result of tissue repair after injury or surgical procedures.

v. CONTRACTION

Experts for plaintiffs in the mesh litigation have claimed that TVT and TVT-O meshes contract significantly in the body. The evidence these experts rely upon are general tissue healing concepts, as well as data from hernia meshes and pelvic organ prolapse meshes. The relevant studies examining this issue for TVT do not support these experts' claims of TVT mesh contraction. Ultrasound studies have found TVT mesh does not contract to any significant degree.[44] [45] Long term data and at least one prospective study demonstrate that TVT does not contract in the body.[46] [47] In addition, examination of mesh on histology slide does not offer a scientifically reliable basis for the opinion that mesh has contracted because the tissue has been fixed in formalin and processed using several chemicals.

vi. NORMAL VAGINA, INNERVATIONS, AND CORRELATION TO PAIN

The vaginal wall consists of smooth muscle, fibroconnective tissue, skin, and ligaments that make up the structure of the vagina. It surrounds the vaginal canal, which connects the cervix to the vulva, the outside of the body. The vaginal wall contains peripheral nerve fibers that serve a normal function for sensation or for autonomic functions. It would be abnormal if no nerve fibers were found in the vaginal wall. Compared to the wall of the cervix and the uterus, the amount of innervation in the vagina is typically increased, which allows easy identification of nerve endings or twigs under the microscope from those histologic sections of the vagina. .

Vaginal pain is a clinical symptom. The contributing factors for the pain are multiple and complex, and in many cases are poorly understood. It is known that neuroma can cause pain. Neuromas are tumors of nerve cells or nerve fibers and can occur with any surgery. I have not seen any evidence of neuroma in more than a hundred mesh specimens in the last 5 years and my review of the literature does not lead me to conclude that neuroma are related to TVT implantation or the mesh. Also, nerve fibers are commonly observed in and around the integrated tissue of those explanted vaginal mesh samples, including those women who did not have pain prior to the surgeries. Presence of nerves in tissue in and around the mesh is not an evidence of painful nerve entrapment. Without evidence of nerve abnormality, finding nerve fibers in vaginal mesh does not correlate to the clinical symptoms of vaginal pain or dyspareunia. Dyspareunia occurs more commonly in postmenopausal women and such conditions are known to be related to the decreased levels of estrogen resulting in cellular atrophy and then reduced elasticity and thinning of the vaginal wall. Dyspareunia may also occur after any kind of surgical procedures in or near the vagina.

In any event, the rates of pain and/or dyspareunia related to TVT or TVT-O are quite low.[48] Experts for mesh plaintiffs acknowledged this in relation to midurethral slings in a recent article by Drs. Blaivas and Iakovlev. In that review article, pain lasting more than 6 weeks following surgery was reported as 1.8% for retropubic midurethral slings and 4.3% for obturator midurethral slings.[49] Another study by Schimpf and others examined many studies looking at synthetic slings, including numerous studies that included TVT and/or TVT-O, and found dyspareunia to occur in 0.00% of patients with retropubic slings and 0.16% with obturator slings.[50]

Plaintiffs' experts such as Dr. Iakovlev have attempted to correlate findings such as inflammation, fibrosis, and foreign body reaction to pain and other clinical symptoms. This runs counter to the published literature involving slings and hernia meshes. Recently, Hill and several other authors compared meshes removed for pain to those removed for reasons other than pain. [51] The authors found no positive associations between inflammation and pain, fibrosis and pain, or foreign body giant cell reaction and pain. Nearly all specimens contained a foreign body reaction to the mesh, both those with pain and those without. This demonstrates that pathologists cannot look at tissue under the microscope and attribute symptoms such as pain to inflammation, fibrosis, or foreign body reaction.

vii. CANCER

In my opinion, there is no evidence to support the belief that TVT mesh is carcinogenic or tumorigenic. There have been numerous studies evaluating the TVT in the nearly 20 years since TVT was introduced; none has described cancers in humans. Further, rat studies on sarcoma formation cannot be extrapolated to the human experience. [52] Recent reviews have found no evidence of a risk of carcinogenicity.[53] [54] [55]

II. RESPONSE TO DR. IAKOVLEV

In his general expert report, Dr. Vladimir Iakovlev presents his own overall understanding of vaginal mesh and the tissue reaction to it. Although Dr. Iakovlev correctly notes many known complications related to the vaginal mesh implants, he omits any reference to the low rates for the complications. This is particularly troubling in light of the low complication rates and high cure rates for TVT and TVT-O.

He provides almost no information about the pictures of patients from whom the meshes were explanted. He presented many photomicrographs in his expert report without specifics of patients' clinical information and tissue conditions. He has used many unverified "methods" either in research or in clinic trying to demonstrate his findings are pathologically meaningful. More strikingly, he attempts to extrapolate from those explanted meshes from unknown sources to support his opinion that TVT and TVT-O meshes are linked to clinical complications due to defective manufacturing or design. This is not reliable science for a number of reasons: 1) the specificity and sensitivity of Dr. Iakovlev's methods used to evaluate the mesh specimens are not verified; 2) Dr. Iakovlev's cohort is mainly derived from litigation meshes he received from Plaintiffs' counsel in various litigations without consideration of many women who received mesh implantation without any complications, and without controlling for symptomology; and 3) his numerous selected photographs of histological examinations do not include any information about the patient's condition or history. Importantly, Dr. Iakovlev's opinions are contrary to the significant medical literature and surgeon specialty organizations that recognize midurethral slings such as TVT and TVT-O as the "gold standard" and standard of care, with low complication rates and high cure rates.

I provide the following overview comments related to the pathologic findings and clinical correlations found in Dr. Iakovlev's general report:

1) Dr. Iakovlev consistently refers to fibrous tissue as "mesh scar" formation, "bridging fibrosis" or "scar encapsulation". He apparently assumes all the integrated tissue into mesh pores represents scar or "bridging fibrosis" surrounding the mesh fibers. I have reviewed all his photomicrographs and have identified good tissue integration, rather than pure scar, in the majority of the pictures he presented. There is clear difference between "bridging fibrosis" or "scar formation" and tissue integration, in which the former two indicate the loss of tissue function, while the later provides good support from the tissue-mesh complex. This support helps the TVT and TVT-O perform their designed function. Dr. Iakovlev claims that fibrous encapsulation and fibrous bridging formation is demonstrated in his photomicrographs in Figure set 2 of his report. Although he did not provide the source for these pictures, I can easily identify good tissue integration without finding any evidence of fibrous encapsulation or "fibrous bridging". This is evidenced by the presence of fibroblasts and microcapillary vessels in addition to the deposition of collagen. There is mild chronic inflammation, which is mainly present adjacent to the mesh fibers. These are normal findings for mesh implantation. Presence of loose connective tissue versus smooth muscle bundles adjacent to the mesh fibers is mainly related to the location of the mesh and the specific conditions of the mesh explants. Both smooth muscle and loose connective tissue can be found within the vagina and the adventitial tissue of the vaginal wall.

2) Dr. Iakovlev described "mesh-scar innervation" and "severe deformation of nerves and formation of neuroma type lesions" in his report (page 15, paragraph 5 and 6). The vaginal wall is innervated with peripheral nerves, both sensory and autonomic, in a normal vagina and it is known that peripheral nerves are able to grow after injury or surgical section. Surgical procedures to treat incontinence cause tissue injury. It is quite common or expected to see nerve endings/fibers or twigs present adjacent to mesh fiber spaces or even within the mesh pores since the pore sizes are large enough to allow good tissue integration. Finding nerve fibers adjacent or within the mesh specimens does not alone correlate with dyspareunia or pelvic/vaginal pain. This is evidenced by the following facts: a) a normal vagina is well innervated, but the majority of women do not have pain; b) published data finds vaginal pain or dyspareunia occurs in a small percentage of patients who received TVT or TVT-O, while explants from such patients demonstrate innervation within the vagina. Therefore, assumptions cannot be made that the presence of nerve equates to risk of pain or pain itself.

3) Dr. Iakovlev includes several photomicrographs of neural ganglia, but he does not explain how this marker of autonomic innervation addresses his opinions regarding pain. If neural ganglia are present in the tissues, then at least some portion of the nerves are autonomic and not sensory. It is unclear how Dr. Iakovlev attempts to differentiate between the types of signals the various nerves send.

4) Dr. Iakovlev presented his pictures with S100 staining showing innervation of vaginal mucosa overlying the mesh (Figure set 5 of his report). As I mentioned earlier that it is a

normal to find nerve endings in vaginal tissue and it is not necessary to use S100 to illustrate the nerve fibers in this setting. In addition, S100 is not specific for nerve staining. This is illustrated by Dr. Iakovlev's figure showing squamous mucosa with similar brown spots as indicated as nerve endings by arrows. It is known that squamous mucosa of the vagina is not innervated. As a trained pathologist, Dr. Iakovlev should understand this. If Dr. Iakovlev really wants to show nerve fibers, he should use the immunohistochemical stain "neurofilament" instead of using S100.

5) Dr. Iakovlev describes "mesh folding and curling" in figure set 10 of his expert report. Dr. Iakovlev's imagined geometry is following fixation in formalin and tissue processing, both of which are known to trained pathologists to distort the size and orientation of tissues. The figure set 10a actually represents normal morphologic appearance of explanted TVT mesh fibers, which can be routinely seen under the microscope. They simply represent different planes of mesh fibers cut on slides. Dr. Iakovlev does not accompany his photomicrographs with any clinical findings of curled, curved, or deformed meshes by clinicians who examined the patients prior to the explanting the specimens to support his histologic interpretations. The right panel of figure set 10b shows a normal explanted mesh after formalin fixation since the color of the sample is brown-grey, which is a classic appearance of formalin fixed tissue samples. All tissue, including explanted meshes with associated tissues, becomes harder after formalin fixation than fresh tissue because part of the water component within cells are removed and the cellular proteins are cross linked. In fact, one of the goals of fixation is to harden the tissue to allow for thin sectioning. It is well known to pathologists that "over-fixation" – which can happen as early as 6-8 hours in formalin – results in hard, brittle tissue. Given this, it is likely that the shrinking and hardening effects of formalin fixation caused what Dr. Iakovlev sees as deformation. It is surprising that Dr. Iakovlev, as a trained surgical pathologist, interpreted these findings as curled deformity.

6) Dr. Iakovlev's report makes very little distinction between meshes treating pelvic organ prolapse and those treating stress urinary incontinence such as TVT and TVT-O. This is potentially important because many of the photomicrographs in his report appear to be from pelvic organ prolapse meshes, not TVT or TVT-O.

7) Dr. Iakovlev asserts that Prolene mesh degrades in vivo. In support of this opinion, he offers photomicrographs of explanted mesh following formalin fixation and tissue processing. Dr. Iakovlev does not offer any scientifically reliable evidence to demonstrate the chemical makeup of the "degradation bark". Thus, he cannot offer reliable opinions that the mesh is degraded polypropylene rather than degenerated collagen. His opinions regarding cracked layers absorbing histology stains because the polypropylene is oxidized is not supported by any reliable evidence and it contradicted by the testing by Ethicon's expert, Dr. Steven MacLean. Finally, he cannot rule out artifact.

In summary, Dr. Iakovlev's review of the histology does not provide scientific support for his general statements.

III. CONCLUSION

Ethicon's TVT and TVT-O are biocompatible for their use in treating stress urinary incontinence. Their use is supported by numerous studies, long-term follow-up data showing very high cure rates, as well as by the preeminent associations of physicians who implant the devices. The TVT and TVT-O meshes elicit an expected inflammatory response that becomes minimal to mild chronic inflammation, foreign body reaction, and minimal to mild degree of fibrosis, all appropriate healing responses. In addition, the mesh pores are large enough to allow appropriate tissue integration and to allow the body's immune response to minimize potential infection. The scientific evidence does not show that the monofilament mesh structure potentiates infection or painful neuromas or causes cancer.

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Wenxin Zheng, MD

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